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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/765,534	01/19/2001	Kari Alitalo	28967/34891A	1420

4743 7590 06/11/2004

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EXAMINER	
MURPHY, JOSEPH F	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 06/11/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/765,534	ALITALO ET AL.	
	Examiner	Art Unit	
	Joseph F Murphy	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *3/29/2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) *1-18 and 25-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-24 and 31-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/26/02 11/1/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Sequence Comparison A*.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I claims 19-24 in the response filed 03/23/2004 is acknowledged. The traversal is on the ground(s) that Groups I-II are identical based on the amendment to the claims. In response to this, the Groups I-II will be examined together. Since new claims 31-33 read on the elected Group, these claims will also be examined. Applicant argues that Groups III-IV can be examined without undue burden because all the Groups were examined together in Application 08/340,011. This is not found persuasive for the following reasons. Applicant's attention is directed to MPEP 808.02 which states that "Where the related inventions as claimed are shown to be distinct under the criteria of MPEP 806.05 (c-i), the examiner, in order to establish reasons for insisting upon restriction, must show by appropriate explanation one of the following: (A) Separate classification thereof; (B) A separate status in the art when they are classifiable together; (C) A different field of search." As set forth in the Restriction requirement, Groups I-II are classified in class 530, subclass 350; Groups III-IV are classified in class 435, subclass 69.1. The separate classification established for each Group demonstrates that each distinct Group requires a separate field of search, and a search of one Group would not reveal art on the other Groups, thus imposing a burden on the examiner. In addition, each Application is examined on its own merits, thus, the Restriction requirement is proper.

The requirement is still deemed proper and is therefore made FINAL.

Information Disclosure Statement

References C61-C68 of 04/26/2002 have been lined through because they are not in the correct format. The citation should include the publication date, pursuant to 37 CFR 1.98.

Claim Objections

Claims 22-23 are objected to because of the following informalities: The claims use the language "includes" instead of the recognized transitional phrase "comprises". Appropriate correction is required.

Claim 24 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 24 is broader in scope than claim 22 from which it depends, therefore it fails to further limit claim 22.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground

provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 19-24, 31-33 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 38-44 of U.S. Patent No. 5,776,755. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 19-24, 31-33 are generic to all that is recited in claims 38-44 of U.S. Patent No. 5776755. That is, claims 38-44 of U.S. Patent No. 5776755 falls entirely within the scope of claims 19-24, 31-33 or, in other words, claims 19-24, 31-33 are anticipated by claims 38-44 of U.S. Patent No. 5776755. Specifically, the '755 patent claims a polypeptide capable of generating an immune response, and which comprises an extracellular domain of a human flt4 receptor, and further wherein the polypeptide comprises amino acids 1-1298 of SEQ ID NO: 2. The instant claims are drawn to flt4 polypeptides consisting of amino acids 1-775 of SEQ ID NO: 2, polypeptides consisting of amino acids 21-775 of SEQ ID NO: 2, polypeptides

comprising amino acids 21-775 of SEQ ID NO: 4. The instantly claimed polypeptides are an obvious variation of the claims as set forth in the '755 patent because the '755 patent which supports flt4 polypeptides consisting of amino acids 1-775 of SEQ ID NO: 2 or polypeptides consisting of amino acids 21-775 of SEQ ID NO: 2 (see claims 42-44) supports polypeptides comprising these sequences (see claim 38).

Claim Rejections - 35 USC § 112 first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 19-22, 24, 31, 33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, which is enabling for a full-length flt4 of SEQ ID NO: 2 or 4, or a flt4 polypeptide comprising amino acids 1-775 of SEQ ID NO: 2 or 4, or a flt4 polypeptide comprising amino acids 21-775 of SEQ ID NO: 4, does not reasonably provide enablement for a flt4 fragment encoded by 200 nucleotides of SEQ ID NO: 1 or 3, or a polypeptide comprising a flt4 extracellular domain fragment, or a polypeptide comprising flt4 peptides obtained by cyanogens bromide cleavage. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are drawn to a flt4 fragment encoded by 200 nucleotides of SEQ ID NO: 1 or 3, or a polypeptide comprising a flt4 extracellular domain fragment, or a polypeptide comprising flt4 peptides obtained by cyanogens bromide cleavage. Claims 19-22, 24, 31, 33 are overly broad since insufficient guidance is provided as to which of the myriad of variant polypeptides will retain the characteristics of flt4. The claims are directed to variant polypeptides. However,

Applicants do not disclose any actual or prophetic examples on expected performance parameters of any of the possible variants of flt4. It is known in the art that even single amino acid changes or differences in the amino acid sequence of a protein can have dramatic effects on the protein's function. For example, as an example of the unpredictable effects of mutations on protein function, Mickle et al. (Mickle JE et al. Genotype-phenotype relationships in cystic fibrosis. Med Clin North Am. 2000 May;84(3):597-607) teaches that cystic fibrosis is an autosomal recessive disorder caused by abnormal function of a chloride channel, referred to as the cystic fibrosis transmembrane conductance regulator (CFTR) (page 597). Several mutations can cause CF, including the G551D mutation. In this mutation a glycine replaces the aspartic acid at position 551, giving rise to the CF phenotype. In the most common CF mutation, delta-F508, a single phenylalanine is deleted at position 508, giving ride to the CF phenotype. Thus showing that even the substitution or deletion of a single amino acid in the entire 1480 amino acid CFTR protein sequence can have dramatic and unpredictable effects on the function of the protein. Additionally, it is known in the art that even a single amino acid change in a protein's sequence can drastically affect the structure of the protein and the architecture of an entire cell. For example, Voet et al. (Voet et al. Biochemistry. 1990. John Wiley & Sons, Inc. pages 126-128 and 228-234) teaches that a single Glu to Val substitution in the beta subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in homozygous individuals, erythrocytes are altered from their normal discoid shape and assume the sickle shape characteristic of sickle-cell anemia, causing hemolytic anemia and blood flow blockages (pages 126-128, section 6-3A and page 230, column 2, first paragraph). Additionally, Yan et al. teaches that in certain cases, a change of only two-amino acid residues in a protein

results in switching the binding of the protein from one receptor to another (Yan et al., Two-amino acid molecular switch in an epithelial morphogen that regulates binding to two distinct receptors. *Science* 290: 523-527, 2000). Since the claims encompass variant polypeptides and given the art recognized unpredictability of the effect of variations on protein function, it would require undue experimentation to make and use the claimed invention. See In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. The claims do not set forth a functional limitation for the variant polypeptides. Claim 20 only contains the limitation wherein the fragment is sufficient to produce an antibody which binds SEQ ID NO: 2 or 4 but not SEQ ID NO: 6. However, this is not a function that the polypeptide performs, and this property would need to be confirmed by further testing. Since the amino acid sequence of a polypeptide determines its structural and functional properties, and the predictability of which amino acids can be substituted is extremely complex and outside the realm of routine experimentation, because accurate predictions of a polypeptide's structure from mere sequence data are limited. Since detailed information regarding the structural and functional requirements of the polynucleotide and the encoded polypeptide are lacking, it is unpredictable as to which variations, if any, meet the limitations of the claims. Applicant is required to enable one of skill in the art to make and use the claimed invention, while the claims encompass polynucleotides and encoded polypeptides which the specification only teaches one skilled in the art to test for functional variants. It would require undue experimentation for one of skill in the art to make and use the claimed polypeptides. Since the claims do not enable one of skill in the art to make and use the claimed polypeptides, but only teaches how to screen for the claimed polypeptides,

and since detailed information regarding the structural and functional requirements of the polypeptides are lacking, it is unpredictable as to which variations, if any, meet the limitations of the claims. Thus, since Applicant has only taught how to test for polypeptide variants of flt4, and has not taught how to make polypeptide variants of flt4, it would require undue experimentation of one of skill in the art to make and use the claimed polypeptides.

Claims 19-22, 24, 31, 33 are rejected, under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The claims are drawn to a flt4 fragment encoded by 200 nucleotides of SEQ ID NO: 1 or 3, or a polypeptide comprising a flt4 extracellular domain fragment, or a polypeptide comprising flt4 peptides obtained by cyanogens bromide cleavage. These are genus claims because the claims are thus directed to variant polypeptides. The specification and claim do not indicate what distinguishing attributes shared by the members of the genus. The scope of the claim includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. The specification and claim do not provide any guidance as to what changes should be made. Structural features that could distinguish compounds in the genus from others in the protein class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because

specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, SEQ ID NO: 2 or 4 is insufficient to describe the genus. The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. In the instant case, the specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the genus of polypeptides. There is no description of the conserved regions that are critical to the structure and function of the genus claimed. There is no description of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Structural features that could distinguish the compounds in the genus from other seven transmembrane region compounds are missing from the disclosure. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polynucleotides and polypeptides encompassed. Thus, no identifying characteristics or properties of the instant polypeptides are provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 20-21, 24, 31, 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Terman et al. (1991).

The claims are drawn to polypeptides comprising a fragment of a flt4 extracellular domain, and to polypeptides which are fragments of flt4. The Terman reference teaches the cloning and expression of a receptor tyrosine kinase, which is 38.3% identical to instantly claimed SEQ ID NO: 4 (see Sequence Comparison A, attached). The polypeptide taught in the Terman reference anticipates the claims because it comprises sequence which are fragments of the extracellular domain of flt4, since there is no minimal length limitation set forth for the fragments which the polypeptides comprise.

Conclusion

No claim is allowed.

References

The Office will no longer be supplying paper copies of U.S. Patents cited in Office Actions. Applicant is advised that the cited U.S. patents and patent application publications are available for download via the Office's PAIR. As an alternate source, all U.S. patents and patent application publications are available on the USPTO web site (www.uspto.gov), from the Office of Public Records and from commercial sources. Applicant may direct inquiries about the use of

the Office's PAIR system to the Electronic Business Center (EBC) at http://www.uspto.gov/ebc/index.html or 1-866-217-9197.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Murphy whose telephone number is (571) 272-0877. The examiner can normally be reached Monday through Friday from 7:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (571) 272-0887.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Joseph F. Murphy, Ph. D.
Patent Examiner
Art Unit 1646
June 7, 2004

Sequence Comparison A

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RESULT 4
VGR2_HUMAN
ID   VGR2_HUMAN     STANDARD;      PRT;  1356 AA.
AC   P35968; O60723; Q14178;
DT   01-JUN-1994 (Rel. 29, Created)
DT   16-OCT-2001 (Rel. 40, Last sequence update)
DT   10-OCT-2003 (Rel. 42, Last annotation update)
DE   Vascular endothelial growth factor receptor 2 precursor (EC 2.7.1.112)
DE   (VEGFR-2) (Kinase insert domain receptor) (Protein-tyrosine kinase
DE   receptor Flk-1).
GN   KDR OR FLK1.
OS   Homo sapiens (Human).
OC   Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
OC   Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
OX   NCBI_TaxID=9606;
RN   [1]
RP   SEQUENCE FROM N.A.
RA   Yin L.Y., Wu Y., Patterson C.;
RT   "Full length human KDR/flk-1 sequence.";
RL   Submitted (DEC-1997) to the EMBL/GenBank/DDBJ databases.
RN   [2]
RP   SEQUENCE FROM N.A.
RC   TISSUE=Umbilical vein;
RA   Yu Y., Whitney R.G., Sato J.D.;
RT   "Coding region for human VEGF receptor KDR (VEGFR-2).";
RL   Submitted (MAY-1998) to the EMBL/GenBank/DDBJ databases.
RN   [3]
RP   SEQUENCE OF 3-1356 FROM N.A.
RC   TISSUE=Umbilical vein;
RX   MEDLINE=92019839; PubMed=1656371;
RA   Terman B.I., Carrion M.E., Kovacs E., Rasmussen B.A., Eddy R.L.,
RA   Shows T.B.;
RT   "Identification of a new endothelial cell growth factor receptor
RT   tyrosine kinase.";
RL   Oncogene 6:1677-1683(1991).
RN   [4]
RP   SEQUENCE OF 1-22 FROM N.A.
RX   MEDLINE=96032749; PubMed=7559454;
RA   Patterson C., Perrella M.A., Hsieh C.M., Yoshizumi M., Lee M.E.,
RA   Harber E.;
RT   "Cloning and functional analysis of the promoter for KDR/flk-1, a
RT   receptor for vascular endothelial growth factor.";
RL   J. Biol. Chem. 270:23111-23118(1995).
RN   [5]
RP   FUNCTION.
RX   MEDLINE=93038639; PubMed=1417831;
RA   Terman B.I., Dougher-Vermazen M., Carrion M.E., Dimitrov D.,
RA   Armellino D.C., Gospodarowicz D., Boehlen P.;
RT   "Identification of the KDR tyrosine kinase as a receptor for vascular
RT   endothelial cell growth factor.";
RL   Biochem. Biophys. Res. Commun. 187:1579-1586(1992).
CC   -!- FUNCTION: RECEPTOR FOR VEGF OR VEGF-C. HAS A TYROSINE-PROTEIN
CC       KINASE ACTIVITY. THE VEGF-KINASE LIGAND/RECEPTOR SIGNALING SYSTEM
CC       PLAYS A KEY ROLE IN VASCULAR DEVELOPMENT AND REGULATION OF
CC       VASCULAR PERMEABILITY.
CC   -!- CATALYTIC ACTIVITY: ATP + a protein tyrosine = ADP + protein
CC       tyrosine phosphate.
CC   -!- SUBCELLULAR LOCATION: Type I membrane protein.
CC   -!- SIMILARITY: Belongs to the Tyr family of protein kinases.
CC       CSF-1/PDGF receptor subfamily.
CC   -!- SIMILARITY: Contains 7 immunoglobulin-like C2-type domains.
CC   ---------------------------------------------------------------------
CC   This SWISS-PROT entry is copyright. It is produced through a collaboration
CC   between the Swiss Institute of Bioinformatics and the EMBL outstation -
CC   the European Bioinformatics Institute. There are no restrictions on its
CC   use by non-profit institutions as long as its content is in no way
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CC   or send an email to license@isb-sib.ch).
CC   ----------------------------------------------------------------------
DR   EMBL; AF035121; AAB88005.1; -.
DR   EMBL; AF063658; AAC16450.1; -.
DR   EMBL; X61656; CAA43837.1; -.
DR   EMBL; L04947; AAA59459.1; -.
DR   EMBL; X89776; CAA61916.1; -.
DR   PIR; JC1402; JC1402.
DR   HSSP; P11362; 1FGK.
DR   Genew; HGNC:6307; KDR.
DR   MIM; 191306; -.
DR   GO; GO:0005887; C:integral to plasma membrane; TAS.
DR   GO; GO:0005021; F:vascular endothelial growth factor receptor. . .; TAS.
DR   GO; GO:0007169; P:transmembrane receptor protein tyrosine kin. . .; TAS.
DR   InterPro; IPR007110; Ig-like.
DR   InterPro; IPR003598; Ig_c2.
DR   InterPro; IPR000719; Prot_kinase.
DR   InterPro; IPR001824; RecepttyrkinsIII.
DR   InterPro; IPR001245; Tyr_pkinase.
DR   InterPro; IPR008266; Tyr_pkinase_AS.
DR   Pfam; PF00047; ig; 6.
DR   Pfam; PF00069; pkinase; 1.
DR   ProDom; PD000001; Prot_kinase; 2.
DR   SMART; SM00408; IGc2; 2.
DR   SMART; SM00219; TyrKc; 1.
DR   PROSITE; PS50835; IG_LIKE; 5.
DR   PROSITE; PS00107; PROTEIN_KINASE_ATP; 1.
DR   PROSITE; PS50011; PROTEIN_KINASE_DOM; 1.
DR   PROSITE; PS00109; PROTEIN_KINASE_TYR; 1.
DR   PROSITE; PS00240; RECEPTOR_TYR_KIN_III; 1.
KW   Angiogenesis; Signal; Transferase; Tyrosine-protein kinase; Receptor;
KW   Transmembrane; Glycoprotein; Phosphorylation; ATP-binding;
KW   Immunoglobulin domain; Repeat.
FT   SIGNAL        1     19       POTENTIAL.
FT   CHAIN        20   1356       VASCULAR ENDOTHELIAL GROWTH FACTOR
FT                                RECEPTOR 2.
FT   DOMAIN       20    764       EXTRACELLULAR (POTENTIAL).
FT   TRANSMEM    765    789       POTENTIAL.
FT   DOMAIN      790   1356       CYTOPLASMIC (POTENTIAL).
FT   DOMAIN       46    110       IG-LIKE C2-TYPE 1.
FT   DOMAIN      141    207       IG-LIKE C2-TYPE 2.
FT   DOMAIN      224    320       IG-LIKE C2-TYPE 3.
FT   DOMAIN      328    414       IG-LIKE C2-TYPE 4.
FT   DOMAIN      421    548       IG-LIKE C2-TYPE 5.
FT   DOMAIN      551    660       IG-LIKE C2-TYPE 6.
FT   DOMAIN      667    753       IG-LIKE C2-TYPE 7.
FT   DOMAIN      834   1162       PROTEIN KINASE.
FT   NP_BIND     840    848       ATP (BY SIMILARITY).
FT   BINDING     868    868       ATP (BY SIMILARITY).
FT   ACT_SITE   1028   1028       BY SIMILARITY.
FT   CARBOHYD     46     46       N-LINKED (GLCNAC. . .) (POTENTIAL).
FT   CARBOHYD     66     66       N-LINKED (GLCNAC. . .) (POTENTIAL).
FT   CARBOHYD     96     96       N-LINKED (GLCNAC. . .) (POTENTIAL).
FT   CARBOHYD    143    143       N-LINKED (GLCNAC. . .) (POTENTIAL).
FT   CARBOHYD    158    158       N-LINKED (GLCNAC. . .) (POTENTIAL).
FT   CARBOHYD    245    245       N-LINKED (GLCNAC. . .) (POTENTIAL).
FT   CARBOHYD    318    318       N-LINKED (GLCNAC. . .) (POTENTIAL).
FT   CARBOHYD    374    374       N-LINKED (GLCNAC. . .) (POTENTIAL).
FT   CARBOHYD    395    395       N-LINKED (GLCNAC. . .) (POTENTIAL).
FT   CARBOHYD    511    511       N-LINKED (GLCNAC. . .) (POTENTIAL).
FT   CARBOHYD    523    523       N-LINKED (GLCNAC. . .) (POTENTIAL).
FT   CARBOHYD    580    580       N-LINKED (GLCNAC. . .) (POTENTIAL).
FT   CARBOHYD    613    613       N-LINKED (GLCNAC. . .) (POTENTIAL).
FT   CARBOHYD    619    619       N-LINKED (GLCNAC. . .) (POTENTIAL).
FT   CARBOHYD    631    631       N-LINKED (GLCNAC. . .) (POTENTIAL).
FT   CARBOHYD    675    675       N-LINKED (GLCNAC. . .) (POTENTIAL).
FT   CARBOHYD    704    704       N-LINKED (GLCNAC. . .) (POTENTIAL).
FT   CARBOHYD    721    721       N-LINKED (GLCNAC. . .) (POTENTIAL).
FT   MOD_RES    1059   1059       PHOSPHORYLATION (AUTO-) (BY SIMILARITY).
FT   CONFLICT      2      2       Q -> E (IN REF. 2).
FT   CONFLICT    772    772       A -> T (IN REF. 3).
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FT   CONFLICT    787    787       R -> G (IN REF. 3).
FT   CONFLICT    835    835       K -> N (IN REF. 3).
FT   CONFLICT    848    848       V -> E (IN REF. 3).
FT   CONFLICT   1347   1347       S -> T (IN REF. 3).
SQ   SEQUENCE   1356 AA;  151526 MW;  59E7C44B05CFEBB3 CRC64;
```

Query Match 38.3%; Score 2762; DB 1; Length 1356;
Best Local Similarity 44.1%; Pred. No. 1.5e-175;
Matches 608; Conservative 203; Mismatches 480; Indels 88; Gaps 26;

```
Qy          1 MQRGAALCLRLWLCLGLLDGLVS--GYSMTPPTLNITEESHVIDTGDSLSISCRGQHPLE 58
              ||    | : ||||:       |     |:  | |:| ::   |    :| |:||||  |:
Db          1 MQSKVLLAVALWLCVETRAASVGLPSVSLDLPRLSIQKDILTIKANTTLQITCRGQRDLD 60

Qy         59 WAWPGAQEAPATGDKDSEDTGVVRDC-EGTDARPYCKVLLLHEVHANDTGSYVCYYKYIK 117
              | ||  |          ||    | :| :|     :|| | : :|  ||||:| |:|:
Db         61 WLWPNNQSG-------SEQRVEVTECSDGL----FCKTLTIPKVIGNDTGAYKCFYR--- 106

Qy        118 ARIEGTTAASSYVFVRDFEQPFINKPDT------LLVNRKDAMWVPCLVSIPGLNVTL-- 169
                |  |:  ||:|:|:  |||           :  |:   : :||| ||  |||:|
Db        107 ---ETDLASVIYVYVQDYRSPFIASVSDQHGVVYITENKNKTVVIPCLGSISNLNVSLCA 163

Qy        170 RSQSSVLWPDGQEVVWDDRRGMLVSTPLLHDALYLQCETTWGDQDFLSNPFLVHITGNEL 229
              |       |||  : || ::|  : : ::  |  : ||    |: : |  ::| : |  :
Db        164 RYPEKRFVPDGNRISWDSKKGFTIPSYMISYAGMVFCEAKINDESYQSIMYIVVVVGYRI 223

Qy        230 YDIQLLPRKSLELLVGEKLVLNCTVWAEFNSGVTFDWDYPGKQAERGKWVPERRSQQTHT 289
              ||: | |   :|| ||||||||||   | | |: |:|:||  : :  | |      |: :
Db        224 YDVVLSPSHGIELSVGEKLVLNCTARTELNVGIDFNWEYPSSKHQHKKLVNRDLKTQSGS 283

Qy        290 ELS---SILTIHNVSQHDLGSYVCKANNGIQRFRESTEVIVHENPFISVEWLKGPILEAT 346
              |:    | |||  |:: | | | | |::|:   : || | ||| ||::       ::|||
Db        284 EMKKFLSTLTIDGVTRSDQGLYTCAASSGLMTKKNSTFVRVHEKPFVAFGSGMESLVEAT 343

Qy        347 AGDELVKLPVKLAAYPPPEFQWYKDGKALSGRH---SPHALVLKEVTEASTGTYTLALWN 403
               | | |::| |   ||||| :|||:|  |   |   : | | : ||:|  || ||: | |
Db        344 VG-ERVRIPAKYLGYPPPEIKWYKNGIPLESNHTIKAGHVLTIMEVSERDTGNYTVILTN 402

Qy        404 SAAGLRRNISLELVVNVPPQIHEKEASSP-SIYSRHSRQALTCTAYGVPLPLSIQWHWRP 462
              :  :::  : ||| ||||| ||   ||   |   : | |||| | :| |  | |:|:
Db        403 PISKEKQSHVVSLVVYVPPQIGEKSLISPVDSYQYGTTQTLTCTVYAIPPPHHIHWYWQL 462

Qy        463 WTPCKMFAQRSLRRRQQQDLMPQCRDWRAVTTQDAVNPIESLDTWTEFVEGKNKTVSKLV 522
                |   |    :     :  | | :||:|      | ||        :|||||||| ||
Db        463 EEEC---ANEPSQAVSVTNPYP-CEEWRSVEDFQGGNKIEVNKNQFALIEGKNKTVSTLV 518

Qy        523 IQNANVSAMYKCVVSNKVGQDERLIYFYVTTIPDGFTIESKPSEELLEGQPVLLSCQADS 582
              || |||||:|||   ||||: ||:| |:|| .|:   |  :|  :  | : | | | ||
Db        519 IQAANVSALYKCEAVNKVGRGERVISFHVTRGPE---ITLQPDMQPTEQESVSLWCTADR 575

Qy        583 YKYEHLRWYRLNLSTLHDAHGNPLLLDCKNV----HLFATPLAASLEEVAPGARHATLSL 638
              :|:| ||:|    |     |       |||:     | ||  : |  ::        | :
Db        576 STFENLTWYKLGPQPLPIHVGELPTPVCKNLDTLWKLNATMFSNSTNDI--------LIM 627

Qy        639 SIPRVAPEHEGHYVCEVQDRRSHDKHCHKKYLSVQALEAPRLTQNLTDLLVNVSDSLEMQ 698
              :   : : :| |||  |||::  :||  : |:|    || :| || :   :: :|:|:
Db        628 ELKNASLQDQGDYVCLAQDRKTKKRHCVVRQLTVLERVAPTITGNLENQTTSIGESIEVS 687

Qy        699 CLVAGAHAPSIVWYKDERLLEEKSGVDLADSNQKLSIQRVREEDAGRYLCSVCNAKGCVN 758
              |  :|   | |:|:||   | | ||: | |:|:|:|||:|| | | |  |:  ||
Db        688 CTASGNPPPQIMWFKDNETLVEDSGIVLKDGNRNLTIRRVRKEDEGLYTCQACSVLGCAK 747

Qy        759 SSASVAVEGSEDKGSMEIVILVGTGVIAVFFWVLLLLIFCNMRRPAHADIKTGYLSIIMD 818
              |   :||:::| ::||:|||| |||:|||:||::|   ::|    ::|||||||:||
Db        748 VEAFFIIEGAQEKTNLEIIILVGTAVIAMFFWLLLVIILRTVKRANGGELKTGYLSIVMD 807

Qy        819 PGEVPLEEQCEYLSYDASQWEFPRERLHLGRVLGYGAFGKVVEASAFGIHKGSSCDTVAV 878
              | |:||:| || | ||||:|||||:|| ||: || ||||:|:|| |||| | ::| ||||
Db        808 PDELPLDEHCERLPYDASKWEFPRDRLKLGKPLGRGAFGQVIEADAFGIDKTATCRTVAV 867

Qy        879 KMLKEGATASEHRALMSELKILIHIGNHLNVVNLLGACTKPQGPLMVIVEFCKYGNLSNF 938
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